



# VERDICT & SUMMARY

## Levetiracetam

(Keppra®)

For the treatment of generalised epileptic seizures

Committee's Verdict: **CATEGORY B (Q4)**

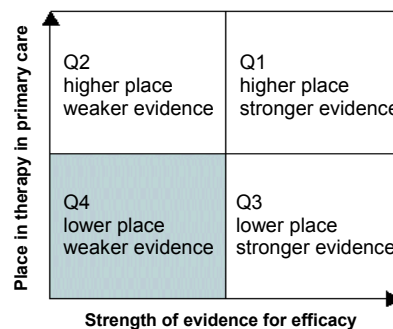
BNF: 4.8.1

**Initiation and stabilisation of treatment with levetiracetam should be the responsibility of the specialist. It is then appropriate for GPs to prescribe levetiracetam for maintenance with the guidance of a shared care agreement. Patients with epilepsy are expected to receive continuing follow-up in secondary care.**

**Category B:** suitable for restricted prescribing under defined conditions

**Q4 rating:** The evidence for the efficacy of levetiracetam for the adjunctive treatment of primary generalised seizures was relatively weak. Two unpublished RCTs showed that levetiracetam was more effective than placebo in reducing seizure frequency and resulted in more seizure-free patients. The lack of published evidence for this indication compared with established drugs gives levetiracetam a low place in therapy.

**The Q rating relates to the drug's position on the effectiveness indicator grid.** The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.



MTRAC updated the review on this drug to include extensions to the licensed indications.

### Licensed indications

Levetiracetam is indicated as monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in patients aged 16 or over with newly diagnosed epilepsy (see verdict sheet VS07/08).

Levetiracetam is indicated as adjunctive therapy in:<sup>1</sup>

- the treatment of partial onset seizures with or without secondary generalisation in patients aged four or over with epilepsy (see VS07/08)
- the treatment of myoclonic seizures in patients aged at least 12 with juvenile myoclonic epilepsy
- the treatment of primary generalised tonic-clonic seizures in people aged at least 12 with idiopathic generalised epilepsy

### Background information

Epilepsy is a serious neurological disorder characterised by recurrent, spontaneous seizures. Seizures are classified into two main groups, generalised and partial seizures, according to the area of the brain in which the abnormal discharge originates. If discharge starts in a localised area of the brain, this is called a partial seizure. Generalised seizures occur following simultaneous activation of both sides of the brain with loss of consciousness from the outset, e.g. tonic-clonic and absence seizures.<sup>2</sup>

Juvenile myoclonic epilepsy usually appears between the ages of 12 to 18 years. It is characterised by single or arrhythmical bilateral myoclonic jerks with retained consciousness. Patients often also have generalised tonic-clonic seizures, and absence seizures are present in one third of cases.<sup>3</sup>

Most patients will respond to the established antiepileptics, e.g. sodium valproate, carbamazepine, or lamotrigine but around 30% often require treatment with more than one antiepileptic drug (AED) and may continue to have seizures despite drug treatment.<sup>4</sup> Several newer AEDs are available as monotherapy or add-on therapy in patients with refractory generalised seizures, e.g. topiramate or levetiracetam.

Levetiracetam is a pyrrolidone derivative chemically unrelated to other AEDs. The mechanism of action of levetiracetam is not known but it does not appear to involve inhibitory or excitatory neurotransmission.

### Clinical efficacy

#### Juvenile Myoclonic Epilepsy (JME)

In an unpublished, double-blind, placebo-controlled RCT (n = 122; 16 weeks),<sup>5,6</sup> levetiracetam 3,000 mg/day was evaluated for the treatment of myoclonic seizures in patients aged 12 to 65 with idiopathic generalised epilepsy including JME. Results showed that 58% of levetiracetam-treated patients responded to treatment (50% reduction in myoclonic-seizure days) compared with 23% of placebo-treated patients

( $p = 0.0002$ ).<sup>5</sup> During treatment, 13 levetiracetam-treated patients (22%) were seizure free compared with two placebo-treated patients (3%).<sup>6</sup>

### Primary Generalised Tonic-Clonic seizures (PGTC)

An unpublished, double-blind placebo-controlled RCT ( $n = 164$ ; 24 weeks)<sup>7</sup> evaluated levetiracetam (maximum dose 3,000 mg/day in adults or 60 mg/kg/day in children) for the treatment of refractory PGTC seizures in patients aged four to 65 years with a diagnosis of idiopathic generalised epilepsy. Results showed that levetiracetam-treated patients had a significantly greater percentage reduction in PCTC seizure frequency from baseline than placebo-treated patients (56% vs. 28%,  $p = 0.0004$ ).<sup>7</sup> The percentage of responders was also significantly higher in the levetiracetam group (72% vs. 45% for placebo,  $p < 0.001$ ). Significantly more levetiracetam-treated patients were seizure-free during treatment (24% vs. 7%,  $p = 0.004$ ).<sup>7</sup>

### Adverse effects

Adverse events observed more frequently with levetiracetam 1,000 mg to 4,000 mg/day were somnolence, asthenia, headache, infection and dizziness. In a safety and tolerability study, the incidence of somnolence was greatest in the highest levetiracetam dosage group (2,000 mg twice daily).<sup>8</sup> Asthenia was most commonly reported in patients in the lower dosage group (1,000 mg twice daily). Adverse events generally appeared within the first month of treatment.<sup>8</sup> Somnolence was the most commonly reported reason for discontinuation in two studies.<sup>8,9</sup> Overall withdrawal rates across the studies were low: 8% to 18% with levetiracetam, and 6% to 14% with placebo. See the Summary of Product Characteristics (SPC) for further details.<sup>1</sup>

### NICE guidance

In March and April 2004, the National Institute for Clinical Excellence (NICE) issued guidance on the use of the newer AEDs for the management of epilepsy in adults and children.<sup>10,11</sup> NICE recommended the use of monotherapy with older AEDs as first line treatment. The newer AEDs should be used, within their licensed indications, in patients who have not benefited from treatment with older AEDs or for whom older drugs are contraindicated. NICE emphasized the importance of appropriate follow-up arrangements and the use of shared care arrangements where necessary for all people with epilepsy.

### Additional information

The recommended initial dose of levetiracetam is 500mg twice daily, which can be increased depending on clinical response and tolerance to a maximum of 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks.<sup>1</sup> Dosage adjustment is required in patients with impaired renal function or severe hepatic impairment. Refer to the SPC for full guidance.<sup>1</sup>

At current prices, one year's treatment costs:

- £636 to £2,168 with levetiracetam 500 mg to 1,500 mg twice daily
- £97 to £195 with gabapentin 300 mg to 2,400 mg daily, in divided doses

### References

1. UCB Pharma Ltd. Keppra. *Summary of Product Characteristics* 2007.
2. Duncan JS, Sander JW, Sisodiya SM *et al.* Adult epilepsy. *Lancet* 2006;**367**:1087-1100.
3. Beghi M, Beghi E, Cornaggia CM *et al.* Idiopathic generalised epilepsies of adolescence. *Epilepsia* 2006;**47 (Suppl.2)**:107-110.
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5. Keppra EMEA/H/C/277/II/61. EMEA. 2006. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/keppra/Keppra%20H-277-II-61-AR.pdf>
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8. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. *Seizure* 2000;**9**:80-87.
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10. Newer drugs for epilepsy in adults. National Institute for Health and Clinical Excellence. March 2004. <http://www.nice.org.uk/guidance/TA76/guidance/pdf/English>
11. Newer drugs for epilepsy in children. National Institute for Health and Clinical Excellence. April 2004. <http://www.nice.org.uk/guidance/TA79/guidance/pdf/English>

Launch date: November 2000

Manufacturer: UCB Pharma Ltd

EU/1/00/146/004, 10, 17, 24, 27

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics  
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

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(THIS VERDICT AND SUMMARY SHEET REPLACES VS05/09)

Date: March 2007

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VS07/09